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(54) Title: COMBINATIONS FOR MANAGING INFLAMMATION AND ASSOCIATED DISORDERS

(57) Abstract: Pharmaceutical compositions comprising at least one analgesic and anti-inflammatory compound(s) that inhibits both cyclooxygenase (COX) and lipooxygenase (LOX) as active agent in combination with at least one another active agent(s) optionally with other pharmaceutically, acceptable excipients is provided. Also described are process for preparation of such compositions and method of using such compositions for the management of inflammation and pain and/or other associated disorders.

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COMBINATIONS FOR MANAGING INFLAMMATION AND ASSOCIATED DISORDERS

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions comprising at least one analgesic and anti-inflammatory compound(s) that inhibits both cyclooxygenase (COX) and lipooxygenase (LOX) as active agent in combination with at least one another active agent(s) optionally with other pharmaceutically acceptable excipients particularly useful in the management of inflammation and pain, and other associated disorders. The present invention also describes process for preparation of such compositions and method of using such compositions for the management of inflammation and pain and/or other associated disorders which comprises administration of an effective amount of such composition to a subject in need thereof.

BACKGROUND OF THE INVENTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are regularly used for the treatment of mild to moderate pain and fever. The analgesic action of this class of compounds results from the inhibition of the enzymatic production of prostaglandins. Prostaglandins are known to play an important role in the inflammation. Since prostaglandins (PG) are produced from arachidonic acid by cyclooxygenases, inhibition of prostaglandin synthesis by cyclooxygenases, especially synthesis of PGE2, PGG2, and PGH2, leads to the treatment of inflammation. There are at least two kinds of cyclooxygenases, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is constitutively present in the gastrointestinal tract and the kidney, and is implicated to be responsible for the maintenance of the physiological homeostasis, such as gastrointestinal integrity and renal function. Interruption of COX-1 activity can lead to life-threatening toxicities to the gastrointestinal tract, such as ulceration and bleeding. Another enzyme, COX-2, also produces these chemical messenger molecules, but the COX-2 enzyme is located specifically in areas of the body that are responsible for inflammation and not in the stomach. COX-2 is induced upon inflammatory stimuli and known to be responsible for progression of inflammation. Thus, selective inhibition of COX-2 over COX-1 is useful for the treatment of inflammation and inflammation-associated disorders without incurring gastrointestinal toxicities. COX-2 inhibitors are thus useful in relieving of pain and swelling of arthritis inflammation and are

implicated to possess a broad therapeutic spectrum besides anti-inflammatory, analgesic, and antipyretic activity. For example, inhibition of COX-2 can prevent growth of certain types of cancer, especially colon cancer (J. Clin. Invest., 99, 2254 (1997)). Another application of a COX-2 inhibitor can be found in the treatment of degenerative chronic neurological disorders, such as Alzheimer's disease (Neurology 48, 626 (1997)). COX-2 inhibition would be useful in reducing the infarct volume accompanying the stroke (J. Neuroscience 17, 2746 (1997)).

Both the conventional NSAIDs and the selective COX-2 inhibitors primarily exert their activity by reducing the production of PGs induced in the inflammatory process. In recent years, it has been clarified that PG synthesis is only one part of the arachidonic acid pathway, this precursor being a substrate that gives rise to many other lipid mediators, such as the LTs (leukotriene) and the LXs (lipoxin). Leukotriene themselves have a major role in the development and persistence of the inflammatory process, and it is now clear that PGs and LTs have complementary effects, whereas the production of LXs can counteract the inflammatory actions of LTs. In view of these concepts, it has been suggested that blocking both LT and PG production might have synergistic effects and achieve optimal anti-inflammatory activity. In addition, taking into account the roles of particularly LTB_4 and cysteinyl LTs (against which neither selective nor non-selective NSAIDs are effective) in the inflammatory process, dual inhibition of the COX and specifically 5-LOX pathways could produce a wider spectrum of anti-inflammatory effects.

It is hypothesized that the undesirable side-effects of NSAIDs are due to the inhibition of COX-1 (constitutive isoform), whereas the beneficial effects are related to the inhibition of COX-2 (inducible isoform). Arachidonic acid can also be converted to leukotrienes (LTs) by the action of 5-lipoxygenase (5-LOX). LTC_4, LTD_4 and LTE_4 are potent bronchoconstrictors, whereas LTB_4 is chemotactic for leukocytes and plays an important role in the development of gastrointestinal ulcers by contributing to the inflammatory process. Thus, developing dual inhibitor compounds that will simultaneously inhibit COX and 5-LOX could enhance their individual anti-inflammatory effects and reduce the undesirable side effects associated with NSAIDs, especially of the gastrointestinal tract. Dual inhibition of COX and 5-LOX may limit the vascular changes seen during inflammation and leukocyte induced GI damage. The most promising COX/5-LOX inhibitor is ML3000 ((2,2-dimethyl-6-(4-chlorophenyl)-

7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)-acetic acid) also known as licofelone.

Spasticity is a disorder of muscle function that causes muscle tightness or spasm. It is the involuntary movement (jerking) of muscles, which occurs when there is damage to the central nervous system. This damage may result from a traumatic brain, injury stroke, tumor, cerebral palsy or multiple sclerosis. Symptoms may include hypertonicity (increased muscle tone), clonus (a series of rapid muscle contractions), exaggerated deep tendon reflexes, muscle spasms, scissoring (involuntary crossing of the legs), and fixed joints. Spasticity may be as mild as the feeling of stiffness or tightness of muscles, or it may be so severe as to produce painful uncontrollable spasms of the extremities, usually of the legs. It may also produce feelings of pain or tightness in and around joints and can also cause low back pain. Tizanidine, a centrally acting a2-adrenergic agonist, is a short-acting drug for the management of spasticity.

Serratiopeptidase is a proteolytic enzyme available for clinical use more than a decade. Serratiopeptidase binds to alpha -2-macroglobulin in the blood in the ratio of 1:1, which helps to mask its antigenicity but retains its enzymatic activity and is slowly, transferred to site of inflammation. Serratiopeptidase hydrolyses bradykinin, histamine and serotonin responsible for oedematic status. Serratiopeptidase reduces swelling improves microcirculation and expectoration of sputum etc. Thus it can be concluded that Serratiopeptidase has anti-inflammatory, anti-oedemic and fibrinolytic activity and acts rapidly on localized inflammation.

Licofelone (ML-3000) is a pyrrolizine derivative orally active dual cyclooxygenase (COX-1 and COX-2) and 5-lipoxygenase inhibitor (dual acting anti-inflammatory drug), under development as an anti-inflammatory and analgesic by the EuroAlliance consortium (Alfa Wassermann/Lacer/Merckle). Licofelone is undergoing evaluation in clinical trials for the indication of osteoarthritis (Laufer S., Expert Opin Investig Drugs, 12(7): 1239-41, 2003), rheumatoid arthritis (Gay R. E., et al., J Rheumatol, 28(9): 2060-5, 2001) and pain. In animal experiments, the compound has antiphlogistic, analgesic, antipyretic, antiasthmatic and antiaggregative activity at a dosage that causes no gastrointestinal damage (Laufer S. et al, Arzneimittelforschung, 44(5): 629-36, 1994). Results of a phase III trial showed that licofelone was at least as effective as naproxen in the long-term treatment of osteoarthritis of the knee (n=704). At dosages of

licofelone 200 and 400 mg/day bid and naproxen 1000 mg/day bid, the greatest improvement in efficacy parameters was achieved with licofelone 400 mg/day bid (Blanco F. J. Et al, Ann Rheum Dis 62(1): 262, 2003). In accordance with the prior art, licofelone doses of 200 and 400 mg/day, administered as divided doses have been found effective for many patients. Following a 200 mg licofelone dose administered twice daily, peak plasma licofelone concentrations of about (1650-1750) ng/ml were reached at (0.74-4) hr post-dose. Licofelone exhibited an elimination half-life (T [sub] 1/2[small beta, Greek]) of about (8.7-11.1) hours (Albrecht W. et al., Annual European Congress of Rheumatology, EULAR 2002, p.abstr. AB0293 12 Jun. 2002). A single dose of licofelone (800-3,200) mg was generally well tolerated in volunteers (Bias P. Et al., Ann Rheum Dis., 62 (1): 479 2003). A combination of a dual 5-lipoxygenase/cyclooxygenase inhibitor with a glucocorticoid is described for the treatment of skin disorders (K, Tramposch, Inflammation, 17, 531 (1993)).

US patent no. 5260451 describes substituted pyrrole compounds and their pharmaceutical applications which are potent inhibitors of lipoxygenase and cyclooxygenase and therefore are suitable to treat the set of rheumatic illnesses and to prevent allergically induced ailments. EP888127 describes the use of a 5-lipoxygenase inhibitor and a cyclooxygenase-2 inhibitor for preparing a medicament to suppress immune, acute or delayed-type hypersensitivity response in a subject. US patent no. 6342510 pertains to a method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising co-administering to the subject, a therapeutically-effective amount of a leukotriene B_4 receptor antagonist and a cyclooxygenase-2 inhibitor. European patent no. 485111 describes the synergistic combination of lipoxygenase inhibitors and NSAID's for the treatment of inflammatory disease.

US publication no. 2003125312 relates to a method for preventing or treating an inflammation-related cardiovascular disorder in a subject in need thereof, which method comprises treating the subject with a an aldosterone antagonist and cyclooxygenase-2 inhibitor combination. US publication no. 20050249806 discloses a pharmaceutical composition comprising at least one acid labile proton pump inhibitor, at least one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitors in the gastric fluid; and at least one nonsteroidal anti-inflammatory drug. PCT publication no. WO2005123130

discloses the use of a combination of a 5-LOX inhibitor and a "bone and cartilage beneficial compound" ("BCBC") selected from the group consisting of bisphosphonates, strontium containing compounds, glucosamine, DMARDs and SERMs for the manufacture of a medicament for treating and/or preventing osteoarthritis, rheumatoid arthritis, osteoporosis or pain, including joint pain in an animal in need thereof.

Still there exists a need for patient compliant, safe and effective compositions that are useful in the management of inflammation, pain and other associated disorders such as muscle tightness or spasms. In order to do so, combination therapies are considered as the best approach to treat various disorders which might lead to a reduction of dose of each active agent and/or decrease in the adverse effects of each drug used in the combination. The present invention discloses combinations comprising a COX & LOX inhibitor and another active agent that might preferably show significant activity in the treatment of inflammation & pain and other associated disorders.

SUMMARY OF THE INVENTION

It is an objective of the present invention to provide pharmaceutical compositions comprising at least one analgesic and anti-inflammatory compound(s) that inhibits both COX and LOX as active agent in combination with at least one another active agent optionally with one or more other pharmaceutically acceptable excipient(s).

It is an objective of the present invention to provide pharmaceutical compositions comprising licofelone or its pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof as the analgesic and anti-inflammatory compound(s) that inhibits both COX and LOX in combination with at least one another active agent optionally with one or more other pharmaceutically acceptable excipient(s).

It is also an objective of the present invention to provide process for the preparation of such pharmaceutical composition, which comprises optionally treating the active agent that inhibits both COX and LOX and at least one another active agent with one or more pharmaceutically acceptable excipient(s) and formulation into a suitable dosage form.

It is yet another objective of the present invention to provide a method of using such composition which comprises administering to a subject in need thereof an effective amount of the composition.

It is a further objective of the present invention to provide pharmaceutical compositions comprising at least one analgesic and anti-inflammatory compound(s) that inhibits both COX and LOX as active agent in combination with at least one another active agent optionally with one or more other pharmaceutically acceptable excipient(s) which are useful in the management of inflammation, pain and other associated disorders such as muscle tightness or spasms, viral infections such as cold and cough, allergic manifestations such as allergic rhinitis, skin rashes with or without swelling, arthritis, asthma, angina, inflammatory bowel disease, Crohn's disease, migraine headaches, Alzheimer's disease, stroke, ischemia and trauma, gastric ulcer induced pain, intermittent or episodic pain, angiogenesis, viral infections, cardiovascular diseases, neoplasia, cancer, bacterial infections, urinary incontinence condition, angiogenesis and the like.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure-1: The figure represents an Isobologram showing analgesic activity of a combination of licofelone (ED_{50} = 31.3 ± 2.27 mg/kg) and nimesulide (ED_{50} = 6.13 ± 1.5 mg/kg) in acetic acid-induced writhing in mice. The oblique line between x- and y-axis is the theoretical additive line. The point '■' in the middle of this line is Theoretical ED_{50} (19.01+ 0.93 mg/kg). 'o' represents experimental ED_{50}.

Figure-2: The figure provides the effect of combination of licofelone ("Lico") and serratiopeptidase ("Serr") against acetic acid-induced writhing in mice.

DETAILED DESCRIPTION OF THE INVENTION

The present invention describes pharmaceutical compositions comprising at least one analgesic and anti-inflammatory compound(s) that inhibits both COX and LOX as active agent in combination with at least one another active agent optionally with one or more other pharmaceutically acceptable excipient(s).

In further embodiment, the analgesic and anti-inflammatory compound(s) that inhibits both COX and LOX within the scope of this invention, includes but is not limited to BW 755C, tepoxalin, ER-34122, licofelone, RWJ 63556, SF&F 86002, or the pharmaceutically acceptable salts, esters, conjugate acids, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, prodrugs, or mixtures thereof. In a preferred embodiment, the active agent that inhibits both COX and LOX is licofelone or its pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues,

enantiomers, tautomeric forms or mixtures thereof.

In an embodiment of the present invention, the another active agent(s) is selected from but not limited to a group comprising antipyretics, aldosterone receptor antagonists, antibiotics, enzymes, antimuscarinic agents, anti-viral agents, protein kinase inhibitors, α2-adrenergic agonist, ACE inhibitors, opioid analgesics, steroids, leukotriene B_4(LTB_4) receptor antagonists, leukotriene A_4 (LTA_4) hydrolase inhibitors, 5-HT agonists, HMG CoA reductase inhibitors, H_2 antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, decongestants, diuretics, anti-histamines, inducible nitric oxide synthase inhibitors, antivirals, antihistamines, Helicobacter pylori inhibitors, bronchodilators, spasmolytics, muscle relaxants, proton pump inhibitors, isoprostane inhibitors, PDE4-inhibitors, NSAIDs, selective or preferential COX-2 inhibitors, COX-1 inhibitors, expectorants, analgesics, antiemetics, urinary acidifiers, antidepressants, antipsychotics, antimigraine agents, enzymes, and the like, or mixtures thereof.

The present invention relates to combinations, compositions, and methods to treat inflammation and pain, and other associated disorders, wherein the said combination comprises at least one analgesic and anti-inflammatory compound that inhibits both COX and LOX, preferably licofelone or its pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof and at least one another active agent.

In a preferred embodiment, another active agent that may be used in combination with licofelone in accordance with this invention and examples from each class are given hereinafter.

Suitable aldosterone receptor antagonists, within the scope of this invention, include but are not limited to eplerenone and spironolactone, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable antibiotics, within the scope of this invention, includes but is not limited to linezolid, amikacin, gentamicin, netilmicin, spectinomycin, tobramycin, imipenem/cilastatin combination, meropenem, cefadroxil, cefazolin, cephalexin, cefaclor, cefotetan, cefoxitin, cefprozil, cefuroxime, loracarbef, cefdinir, cefixime, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftozoxime, ceftriaxone, cefepime, azithromycin, clarithromycin, dirithromycin, penicillin G, cloxacillin, dicloxacillin,

nafcillin, oxacillin, amoxicillin, amoxicillin/clavulanic acid combination, ampicillin, ampicillin/sulbactam combination, mezlocillin, piperacillin, piperacillin/tazobactam combination, ticarcillin, ticarcillin/clavulanate combination, nalidixic acid, ciprofloxacin, enoxacin, lomefloxacin, norfloxacin, ofloxacin, levofloxacin, sparfloxacin, alatrofloxacin, gatifloxacin, moxifloxacin, trimethoprim/sulfamethoxazole combination, sulfisoxazole, sulfamethoxazole, doxycycline, minocycline, tetracycline, chloramphenicol, clindamycin, quinupristin/dalfopristin combination, fosfomycin, nitrofurantoin, rifampin, trimethoprim, vancomycin, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable enzymes, within the scope of this invention, include but are not limited to serratiopeptidase, trypsin, chymotrypsin, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable anti-muscarinic agent, within the scope of this invention, includes but is not limited to alvameline chloride, bethanechol chloride, darifenacin chloride, dicyclomine hydrochloride, emepronium carrageenate, hyoscyamine sulfate, imipramine hydrochloride, oxybutynin chloride, S-oxybutynin chloride, propantheline bromide, propiverine chloride, revatropate chloride, temiverine chloride, terodiline chloride, tolterodine tartrate, trospium chloride, vamicamide chloride, zamifenacin chloride, AH-9700, FK-584, J-104135, KRP-197, YM905, YM-46303, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

Suitable anti-viral agents, within the scope of this invention, includes but is not limited to ganciclovir, foscarnet, cidofovir, acycloguanosine, trifluorothymidine, acyclovir, famciclovir, abacavir, oseltamivir, stavudine, interferon alfa, atevirdine, efavirenz, ribavirin, ritonavir, rimantidine, amantidine, didanosine, vidarabine, valaciclovir, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or combination thereof. Suitable protein kinase inhibitors, within the scope of this invention, includes but is not limited to adaphostin, AG 490, AG 825, AG 957, AG 1024, aloisine, alsterpaullone, aminogenistein, apigenin, arctigenin, AY-22989, bisindolylmaleimide IX, chelerythrine, edelfosine, erbstatin analog, ET18OCH3, erlotinib, fasudil, gefitinib, Imatinib, H-89, HA-1004, HA-1077, hydroxyfasudil, indirubin-3'-oxime, 5-Iodotubercidin, kenpaullone, KN-62, KY12420, LFM-A13, luteolin, LY-294002, mallotoxin, ML-9, NSC-154020, NSC-226080, NSC-664704, NSC-680410, NU6102, olomoucine, PD153035, PD98059, PD169316, phlorizin, piceatannol, picropodophyllin,

PP1, PP2, purvalanol A, quercetin, rapamycin, Ro 31-8220, roscovitine, rottlerin, SB202190, SB203580, sirolimus, SL327, SP600125, staurosporine, STI-571, SU1498, SU4312, SU6656, syk inhibitor, Triciribine, Tyrphostin AG 490, Tyrphostin AG 825, Tyrphostin AG 957, Tyrphostin AG 1024, U0126, wortmannin, Y-27632, ZD1839, ZM 252868, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

Suitable α2-adrenergic agonist, within the scope of this invention, includes but is not limited to clonidine, muscle relaxants such as tizanidine, UK14304, brimonidine, apraclonidine, guanfacine, guanabenz, phenylephrine, methoxamine, metaraminol, ephedrine, oxymetazoline, naphazoline, tetrahydrozoline, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable ACE inhibitors, within the scope of this invention, includes but is not limited to Benazepril, Captopril, Cilazapril, Enalapril, Fosinopril, Lisinopril, Perindopril, Quinapril, Ramipril and Trandolapril, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable opioid analgesics, within the scope of this invention, includes but is not limited to alfentanil, allylprodine, alphaprodine, anileridine, 3-benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narcine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenmorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable steroids, within the scope of this invention, includes but is not limited to cortisone, cortisol, corticosterone, hydrocortisone, hydrocortisol, prednisone, prednisolone, dexamethasone, beclomethasone, betamethasone, mometasone, budesonide, triamcinolone acetonide, fluticasone, ciclesonide, betametasone, or pharmaceutically

acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

Suitable LTB_4 receptor antagonists include, but are not limited to ebselen, linazolast, ontazolast, Bay-x-1005, BI-RM-270, CGS-25019C, ETH-615, TMK-688, LY 213024, LY 210073, LY 223982, LY 233469, LY 255283, LY 264086, LY 292728 and LY 293111; ONO-LB457, ONO-4057, and ONO-LB-448, S-2474, calcitrol, PF 10042, RP 66153, SC-53228, SC-41930, SC-50605, SC-51146, SC-53228, SB-201146, SB-209247, SKF-104493, SM 15178, TMK-688, BPC-15, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable leukotriene A_4 (LTA_4) hydrolase inhibitors include, but are not limited to RP-64966, (S,S)3-amino(4-benzyloxyphenyl)hydroxybutyric acid benzyl] ester, N-(2(R)-(cyclohexylmethyl) (hydroxycarbamoyl)propionyl)-L-alanine, 7-(4-(4-ureidobenzyl)phenyl) heptanoic acid and 3-(3(IE,3E-tetradecadienyl) oxiranyl)benzoic acid lithium salt, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable 5-HT agonists include, but are not limited to rizatriptan, sumatriptan, naratriptan, zolmitriptan, eleptriptan, almotriptan, ergot alkaloids, L-741604, and SB-220453, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

Suitable HMG CoA inhibitors include, but are not limited to simvastatin, pravastatin, lovastatin, mevastatin, fluvastatin, atorvastatin, cerivastatin, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable H_2 antagonists include, but are not limited to cimetidine, roxatidine, ranitidine, famotidine, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable antineoplastic agents include, but are not limited to antimetabolites, 5-FU-fibrinogen, acanthifolic aminothiadiazole, altretamine, anaxirone, aclarubicin, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable antiplatelet agents include, but are not limited to aspirin, ticlopidine, dipyridamole, clopidogrel, glycoprotein 11b/111a receptor antagonists, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable thrombin inhibitors include, but are not

limited to N-((l -(aminoiminomethyl) piperidinyl)methyl)-N-(3,3-diphenylpropinyl)-L-proline amide), 3-(2-phenylethylamino) methyl- 1-(2-aminomethyl methylene-carboxamidomethylpyridinyl) pyrazinone, 3-(2-phenethylamino)6-methyl- 1 -(2-aminomethyl methylene carboxamido methyl pyridinyl)pyridinone, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof. Suitable decongestants include, but are not limited to phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, epinephrine, naphazoline, xylometazoline, propylhexedrine, levodesoxyephedrine, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

Suitable diuretics include, but are not limited to amanozine, amiloride, arbutin, chlorazanil, ethacrynic acid, etozolin, hydracarbazine, isosorbide, mannitol, metochalcone, muzolimine, ticrynafen, triamterene, bendroflumethiazide, chlorothiazide, furosemide, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable proton pump inhibitors include, but are not limited to omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable PDE_4-inhibitors include, but are not limited to CDC-998, IC-485, CC-1088, SCH351591, V11294A, AWD-12-281, AWD-12-343, Cipamfylline, Atizoram, CDC-801, Lirimilast, Piclamilast, Cilomilast, and Roflumilast, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

Suitable antihistamines include, but are not limited to astemizole, azatadine, brompheniramine, buclizine, carbinoxamine, cetirizine, chlorpheniramine, clemastine, cyclizine, cyproheptadine, dexchlorpheniramine, dimenhydrinate, diphenhydramine, diphenylpyraline, doxylamine, fexofenadine, hydroxyzine, loratadine, meclizine, methapyrilene, methdilazine, orphenadrine, pheniramine, promethazine, pyrilamine, terfenadine, trimeprazine, tripelennamine, triprolidine, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable NSAIDs include, but are not limited to aceclofenac, diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, meclofenamate, naproxen, nabumetone, nimesulide, phenylbutazone, piroxicam, sulindac, suprofen, tolmetin, indomethacin, or

pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable COX-2 inhibitors in the present invention include, but are not limited to celecoxib, rofecoxib, valdecoxib, COX 189, etoricoxib, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable bronchodilators include, but are not limited to fenoterol, metaproterenol, procaterol, salbutamol, terbutaline, ipratropium bromide, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. Suitable muscle relaxants in the present invention include, but are not limited to robaxin, robaxisal, succinylcholine, tubocurarine, metocurine, atracurium, cisatracurium, mivacurium, doxacurium, pancuronium, vercuronium, pipecuronium, rocuronium, gallamine, cyclobenzaprine, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof. In one embodiment, the licofelone can be administered in combination with an antipyretic and/or an enzyme and/or a NSAID and/or an antihistamine and/or a muscle relaxant.

In an embodiment of the present invention, the pharmaceutical compositions of present invention further comprises of one or more pharmaceutically acceptable excipient(s) or carrier(s). Examples of these excipients include but not limited to fillers or diluents such as lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose, dibasic calcium phosphate, sucrose-based diluents, confectioner's sugar, monobasic calcium sulfate monohydrate, calcium sulfate, calcium lactate, dextrose, dextran, dextrates, inositol, hydrolyzed cereal solids, amylose, powdered cellulose, calcium carbonate, cellulose powder, starches, pregelatinized starch, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol glycine, or bentonite, and the like; binders such as acacia, alginic acid and salts thereof, cellulose derivatives, methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, magnesium aluminum silicate, polyethylene glycol, gums, polysaccharide acids, bentonites, hydroxypropyl methylcellulose, gelatin, polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer, crospovidone, povidone, polymethacrylates, hydroxypropylmethylcellulose, hydroxypropylcellulose, starch, pregelatinized starch, ethylcellulose, tragacanth, dextrin, microcrystalline cellulose, sucrose, or glucose, and the like; disintegration agents such as starches, pregelatinized corn starch, pregelatinized starch, celluloses, cross-linked carboxymethylcellulose, crospovidone, crosslinked polyvinylpyrrolidone, calcium or a sodium alginate complex,

clays, alginates, gums, or sodium starch glycolate, and any disintegration agents used in tablet preparations;; stabilizers such as antioxidants, buffers, or acids, and the like; lubricants such as magnesium stearate, calcium hydroxide, talc, colloidal silicon dioxide, sodium stearyl fumarate, hydrogenated vegetable oil, stearic acid, glyceryl behenate, magnesium, calcium and sodium stearates, stearic acid, talc, waxes, Stearowet, boric acid, sodium benzoate, sodium acetate, sodium chloride, DL-Ieucine, polyethylene glycols, sodium oleate, or sodium lauryl sulfate, and the like; wetting agents such as oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, sodium oleate, or sodium lauryl sulfate, and the like; anti-adherents or glidants such as talc, corn starch, DL-Ieucine, sodium lauryl sulfate, and magnesium, calcium, or sodium stearates, and the like; solubilizers such as polyethylene glycol and their derivatives, polyoxyethylene alkyl ethers, polyvinylpyrrolidone, polar solvent; and the like used either alone or in combination thereof; carriers such as acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, sodium caseinate, soy lecithin, sodium chloride, tricalcium phosphate, dipotassium phosphate, sodium stearoyllactylate, carrageenan, monoglyceride, diglyceride, or pregelatinized starch, and the like; antioxidants, vehicles, buffers, preservatives, complexing agents, colorants, flavorants, pH modifiers, surfactants, viscosifiers, gelling agents, tonicity modifiers, lipid component, emulsifiers, coating agents, plasticizers, organic solvents, stabilizers, chelating agents, or mixtures thereof.

Pharmacological study

A study was conducted to find out the analgesic, anti-inflammatory effects and other associated effects of the COX and LOX inhibitor e.g. licofelone in combination with either of another active agent selected from nimesulide and serratiopeptidase by isobolographic analysis using Swiss mice (18-22 g) of either sex wherein each group comprises 3-6 mice. The drugs/active agents used in study are Licofelone (B.No.TD/0020/06/05/RI); Nimesulide (B.No.NM/15510B) and Serratiopeptidase tablets containing 10 mg of serratiopeptidase (Lyser forte, Comed chemicals limited, Baroda). The studies are described below:

1) The effects of licofelone with nimesulide were studied. The doses of licofelone and nimesulide used were 1/2, 1/4, 1/8 & 1/16 fraction of ED_{50} of licofelone and nimesulide. ED_{50} (Effective Dose 50 is the amount of drug required to produce a

specified effect in 50% of an animal population) of licofelone (31.33 ± 2.27 mg/kg, po) was selected from previous in-house studies and ED_{50} of nimesulide (6.31 ± 1.5 mg/kg, po) was selected from Jain et al., 2001. In combination, licofelone and nimesulide were administered in the following doses:

Table-1: ED_{50} values for licofelone & nimesulide combination

ED_{50} fraction	Dose of licofelone (mg/kg)	Dose of nimesulide (mg/kg)	Total dose (mg/kg)
1 / 2	3.15	15.66	18.81
1 / 4	1.57	7.83	9.40
1 / 8	0.76	3.91	4.67
1 / 16	0.38	1.95	2.33

2) The effects of licofelone with serratiopeptidase were studied. The doses of licofelone and serratiopeptidase used were the varying fractions 1/2, 1/ 4, 1/8 of ED_{50} of licofelone combined with fixed dose of serratiopeptidase i.e. 40 mg/kg. ED_{50} of serratiopeptidase was determined experimentally using doses of 2, 5, 10, 20, 40, 80 mg/kg in acetic acid-induced writhing in mice. Depending upon ED_{50} value, combination was decided. Administration route was per oral (po).

Experimental Protocols:

Drug preparation: The drugs were suspended in 0.5 % w/w CMC containing 1% v/v tween 80.

Acetic acid-induced writhing assay (abdominal constriction test in mice):

Abdominal constrictions (development of tension in abdominal muscles, elongation of the body and hind limb, arching of back) due to injection of acetic acid (1 % v/v, 10 mL kg^{-1}, ip) were recorded in mice as a response to nociceptive stimuli for 20 minutes after 3 minutes of the administration of acetic acid. Acetic acid (ip) was administered 30 minutes after oral dosing with drug alone or the prepared combination of drugs.

ED_{50} calculation: The number of writhes (a quantal response) was converted to percent maximum possible effect (%MPE), a graded response. The probit value for %MPE by each dose was obtained from probit table. By regression analysis methodology, log dose producing 50% effect was obtained. Finally, the antilog of the log dose was used to generate ED_{50} value.

Isobolographic analysis: The isobologram was constructed by connecting the ED_{50} value of the corresponding extract plotted one on abscissa and the other on ordinate to obtain the additive line. The theoretical additive dose (ED_{50add}) for a combination was calculated from the following equation:

$$Ed_{50add} = Z_1 / (p_1 + Rp_2)$$ where,

Z_1 is the ED_{50} of one drug,

p_1 and p_2 are the proportions of each component in the mixture respectively, and

R is the relative potency of the drugs.

Both the theoretical and experimental ED_{50} values were plotted in the form of graphs termed as isobolograms.

Results and discussion:

1) Licofelone & Nimesulide combination: The ED_{50} values for licofelone & nimesulide combination are shown in Table-1 and isobolographic analysis of the combination is represented in Figure-1. The isobologram (Figure-1) shows that experimental ED_{50} is different from that of theoretical ED_{50}. The experimental ED_{50} of the combination of licofelone & nimesulide shows significant effect against acetic acid-induced writhing in mice.
2) Licofelone & serratiopeptidase combination: The combination of licofelone & serratiopeptidase at all the doses inhibited the writhing response in mice at each dose level (Figure-2) and is hence effective.

In an embodiment of the present invention is provided a process for the preparation of such composition which comprises optionally treating the active agent that inhibits both COX and LOX and at least one another active agent with one or more pharmaceutically acceptable excipient(s) and formulation into a suitable dosage form. In an embodiment, the process for the preparation of such composition comprises the following steps:

i) treating the COX and LOX inhibitor with one or more pharmaceutically acceptable excipient(s),
ii) treating the another active agent with one or more pharmaceutically acceptable excipient(s),
iii) formulating the compositions of step (i) and (ii) to obtain a suitable dosage form.

In another embodiment, the COX and LOX inhibitor and/or the other active agent is

formulated as an immediate release composition or a modified release composition or a combination thereof such as partly immediate release and partly modified release. The controlled release composition may be in the form of extended release, sustained release, prolonged release, delayed release, programmed/timed release, pulsatile release or mucoadhesive/bioadhesive compositions or combinations thereof. The modified release compositions can be prepared by using release controlling polymers such as cellulosic polymers, acrylate/methacrylate polymers/copolymers, alginates, gums, carbomers, lipophilic compounds such as waxes, glyceryl behenate, and the likes, or mixtures thereof, or any polymer known to the art to control the rate of release of active agent(s). The combinations of the present invention can be provided as pharmaceutically acceptable formulations using formulation methods known to those of ordinary skill in the art. These formulations can be administered by standard routes. In general, the combinations may be administered by the oral, topical, transdermal, rectal or parenteral (e.g., intravenous, subcutaneous or intramuscular) route. In addition, the combinations may be incorporated into biodegradable polymers allowing for sustained release of the compound, the polymers being implanted in the vicinity of where drug delivery is desired, for example, at the site of a tumor.

The formulations include those suitable for oral, rectal, ophthalmic, (including intravitreal or intracameral) nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intratracheal, and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by conventional pharmaceutical techniques. Such techniques include the step of bringing into association the active agent(s) and the pharmaceutical excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association the active agents with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product to produce a suitable pharmaceutical dosage form.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, patches or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil emulsion and as a bolus, etc. In a further embodiment, the composition of the present invention is in the form of tablets. The tablets can be prepared by either direct compression,

dry compression (slugging), or by granulation. In a preferred embodiment of the present invention, the oral composition is prepared by direct compression or compaction granulation. The granulation technique is either aqueous or non-aqueous. The non-aqueous solvent used is selected from a group comprising ethanol, isopropyl alcohol or methylene chloride. In an embodiment, the compositions of the present invention are in the form of compressed tablets, moulded tablets, products prepared by extrusion or film cast technique, and the like. In an embodiment, the compositions of the present invention are in the form of compacted tablets/minitablets, compressed tablets/minitablets, or moulded tablets/minitablets prepared by extrusion or film cast technique, and the like. The tablets/minitablets may be monolithic or layered. The tablets/minitablets may be optionally coated with a functional or nonfunctional coating. In an embodiment the functional coating comprises additionally an active agent. The tablets may be formulated as layered tablets comprising at least two layers wherein the same active agent is present in all the layers exhibiting different release profiles or one or more additional active agent(s) is present in the layers exhibiting different release profiles. The tablet/minitablets may be optionally filled into capsules.

Formulations suitable for topical administration in the mouth include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active agent in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the ingredient to be administered in a suitable liquid carrier. Formulations suitable for topical administration to the skin may be presented as ointments, creams, gels and pastes comprising the ingredient to be administered in a pharmaceutical acceptable carrier. A preferred topical delivery system is a transdermal patch containing the ingredient to be administered. Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate. Formulations suitable for nasal administration comprises a carrier and is in the form of a dry powder inhaler (DPI), metered dose inhaler (MDI), nasal spray, nasal drops, and the like; and includes aqueous or oily solutions of the active agent(s). Formulations suitable for vaginal administration may be presented as pessaries, tamports, creams, gels, pastes, foams or spray formulations containing in addition to the active agent(s) such carriers as are known in the art to be appropriate. Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the

formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials, and may be stored in freeze-dried (lyophilized) conditions requiring only the addition of the sterile liquid carrier, for example, water for injections, immediately prior to use. The injections are preferably administered through the intra-muscular or intra-venous routes. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the administered active agent(s). It should be understood that in addition to the ingredients, particularly mentioned above, the formulations of the present invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include flavoring agents and/or colorants. The amount of each active agent(s) in the combination or composition that is required to achieve the desired biological effect will depend primarily on the type of disease or disorder being treated and the treatment regimen.

In an embodiment, a combination comprising a licofelone and another active agent is used in treating inflammation and other associated disorders, but not limited to the treatment of arthritis, rheumatoid arthritis, spondyloarthopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. The invention would also be useful in the treatment of cold & cough, spasms, asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin related conditions such as psoriasis, eczema, burns and dermatitis. The invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention or treatment of cancer, such as colorectal cancer. The invention would be useful in treating inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, viral infections and cystic fibrosis; central nervous system disorders such as cortical dementias including Alzheimer's disease; allergic

diseases, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis and central nervous system damage resulting from stroke, ischemia and trauma, psoriasis, hypersensitivity disorders, and the like.

In a preferred embodiment, the present invention provides pharmaceutical compositions comprising at least one analgesic and anti-inflammatory compound(s) that inhibits both COX and LOX as active agent in combination with at least one another active agent optionally with one or more other pharmaceutically acceptable excipient(s) which are useful in the management of inflammation, pain and other associated disorders such as muscle tightness or spasms, viral infections such as cold and cough, allergic manifestations such as allergic rhinitis, skin rashes with or without swelling, arthritis, asthma, angina, inflammatory bowel disease, Crohn's disease, migraine headaches, Alzheimer's disease, stroke, ischemia and trauma, gastric ulcer induced pain, intermittent or episodic pain, angiogenesis, viral infections, cardiovascular diseases, neoplasia, cancer, bacterial infections, urinary incontinence condition, angiogenesis and the like.

In an embodiment, the amount of the active agents that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The combinations of the present invention are intended to include administration of each active agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to include co-administration of these agents in a substantially simultaneous manner, such as in a single tablet of capsule having a fixed ratio of these active agents or in multiple, separate tablets or capsules for each agent or separate minitablets for each active agent filled into a single capsule.

The combinations of the present invention may have one or more number of uses. For example, through dosage adjustment and medical monitoring, the individual dosages of the active agents used in the combinations of the present invention may be lower than are typical for dosages of the active agents when used in monotherapy. The dosage lowering may further provide advantages including reduction of side effects of the individual active agent(s) when compared to monotherapy. In addition, fewer side

effects of the combination therapy compared with monotherapies may lead to greater patient compliance with therapy regimens.

In a further embodiment, the present invention provides a method of using such composition which comprises administering to a subject in need thereof an effective amount of the composition. The pharmaceutical compositions are particularly useful in the management of inflammation, pain and other associated disorders such as muscle spasms, arthritis, asthma, angina, inflammatory bowel disease, Crohn's disease, migraine headaches, Alzheimer's disease, stroke, ischemia and trauma, gastric ulcer, intermittent or episodic pain, angiogenesis, viral infections, cardiovascular diseases, neoplasia, cancer, bacterial infections, and the like. The compositions of the present invention are particularly useful against prostaglandin and/or leukotriene mediated disorders.

In yet another embodiment, the combination of COX and LOX inhibitor such as licofelone with collagenase inhibitors and cytotoxic agents can be used in the treatment of non-small-cell lung cancers. The combinations of the present invention would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis; in the treatment of certain central nervous system disorders such as cortical dementias including Alzheimer's disease; as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less undesirable side effects; in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis and central nervous system damage resulting from stroke, ischemia and trauma, and the like.

The examples given below serve to illustrate embodiments of the present invention. However they do not intend to limit the scope of present invention.

EXAMPLES

Example 1: Tablet

S. No.	Ingredients	Quantity (mg/tablet)
1.	Licofelone	200
2.	Nimesulide (micronized)	100
3.	Microcrystalline cellulose (Avicel PH 101)	50
4.	Lactose monohydrate	35
5.	Starch 1500	30

6.	Sodium lauryl sulphate	20
7.	Croscarmellose sodium	15
8.	Silicon dioxide	5
9.	Starch	20
10.	Purified water	q.s. (lost in processing)
11.	Croscarmellose sodium	15
12.	Magnesium stearate	5
13.	Talc	5

Procedure:

i) Licofelone, Nimesulide, Microcrystalline cellulose, Lactose, Starch, Sodium lauryl sulphate, Croscarmellose sodium and Silicon dioxide were blended together.

ii) Blend of step (i) was passed through #40 sieve.

iii) Paste was prepared by dispersing starch into hot purified water.

iv) Mixture of step (ii) was granulated with the paste of step (iii).

v) Granules of step (iv) were passed through #10 sieve and were dried.

vi) Dried granules of step (v) were passed through #22 sieve.

vii) Croscarmellose sodium, magnesium stearate and talc were passed through #60 sieve and blended with the granules of step (vi) and compressed into tablets.

Example 2: Tablet

S. No.	Ingredients	Quantity (mg/tablet)
1.	Licofelone	200
2.	Serratiopeptidase enteric coated granules	18
3.	Lactose	189
4.	Starch	40
5.	Sodium starch glycolate	40
6.	Magnesium stearate	8
7.	Talc	5

Procedure:

i) Licofelone, Lactose, Starch, Part of Sodium starch glycolate and part of Magnesium stearate were mixed and passed through #40 sieve.

ii) Bulk of step (i) was compressed into compacts.

iii) Compacts of step (ii) were passed through #12 and then through #20 sieve.

iv) Serratiopeptidase enteric coated granules were passed through #30 sieve and mixed

with the granules of step (iii).

v) Remaining part of Sodium starch glycolate, remaining part of Magnesium stearate and Talc were sifted through #60 sieve and mixed with the granules of step (iv).

vi) Blend of step (v) were compressed into tablets.

Example 3: Tablet

S. No.	Ingredient	Quantity (mg/tablet)
1.	Licofelone	150.0
2.	Roflumilast	0.5
3.	Microcrystalline cellulose	144.5
4.	Starch	40.0
5.	Sodium alginate	4.0
6.	Sodium dioctyl sulfosuccinate	1.0
7.	Magnesium stearate	4.0
8.	Colloidal silicon dioxide	6.0
9.	Croscarmellose sodium	10.0
10.	Purified water	q.s. (lost in processing)

Procedure:

i) Licofelone, Roflumilast, Microcrystalline cellulose & Starch were sifted through #40 mesh sieve and mixed.

ii) Sodium alginate & Sodium dioctyl sulfosuccinate were dissolved in Purified water and granulated the above mixture.

iii) The granules of step (ii) were dried, sifted and blended with Magnesium stearate, Colloidal silicon dioxide & Croscarmellose sodium.

iv) The material of step (iii) was compressed into tablets.

Example 4: Tablet

S. No.	Ingredient	Quantity (mg/tablet)
1.	Tepoxalin	100.0
2.	Serratiopeptidase	15.0
3.	Paracetamol	500.0
4.	Lactose monohydrate	200.0
5.	Polyvinylpyrrolidone	40.0
6.	Sodium starch glycollate	60.0

7.	Magnesium stearate	4.0
8.	Colloidal silicon dioxide	6.0
9.	Purified water	q.s. (lost in processing)

Procedure:

i) Tepoxalin, Serratiopeptidase, Paracetamol, Lactose monohydrate and Sodium starch glycollate were sifted through #40 mesh sieve and mixed.

ii) Polyvinylpyrrolidone was dissolved in Purified water and granulated the above mixture.

iii) The granules of step (ii) were dried, sifted and blended with Magnesium stearate and Colloidal silicon dioxide.

iv) The material of step (iii) was compressed into tablets.

Example 5: Capsule

S.No.	Ingredient	Quantity (mg/capsule)
1.	Licofelone	150.0
2.	Rabeprazole	40.0
3.	Lactose monohydrate	250.0
4.	Magnesium stearate	4.0
5.	Colloidal silicon dioxide	6.0

Procedure:

i) Licofelone, Rabeprazole and Lactose monohydrate were sifted through #30 mesh sieve and mixed.

ii) Magnesium stearate & Colloidal silicon dioxide were sifted through #40 mesh sieve and mixed.

iii) The materials of step (i) & (ii) were mixed together.

iv) The material of step (iii) was filed into capsules.

Example 6: Tablet

S. No.	Ingredient	Quantity (mg/tablet)
1.	Licofelone	150.0
2.	Tizanidine	15.0
3.	Microcrystalline cellulose	150.0
4.	Lactose monohydrate	150.0
5.	Hydroxypropyl methylcellulose	12.0

6.	Croscarmellose sodium	10.0
7.	Hydrogenated castor oil (Lubritab®)	4.0

Procedure:

i) Licofelone, Tizanidine, Microcrystalline cellulose, Lactose monohydrate, Hydroxypropyl methylcellulose & Croscarmellose sodium were sifted through #30 mesh sieve and mixed.

ii) Hydrogenated castor oil was sifted through #40 and mixed with the material of step (i).

iii) The material of step (ii) was compressed into tablets.

Example 7: Tablet

S. No.	Ingredient	Quantity (mg/tablet)
1.	Licofelone	300.0
2.	Cetirizine	10.0
3.	Mannitol	240.0
4.	Xanthan gum	60.0
5.	Sodium carboxymethyl cellulose	40.0
6.	Sodium starch glycollate	40.0
7.	Magnesium stearate	4.0
8.	Colloidal silicon dioxide	6.0
9.	Purified water	q.s. (lost in processing)

Procedure:

i) Licofelone, Cetirizine, Mannitol & Sodium starch glycollate were sifted through #30 mesh sieve and mixed.

ii) Xanthan gum & Sodium carboxymethyl cellulose were dispersed in Purified water and granulated the above mixture.

iii) Magnesium stearate & Colloidal silicon dioxide were sifted through #40 mesh sieve

iv) The granules were dried, sifted and blended with the material of step (iii).

v) The material of step (iv) was compressed into tablets.

Example 8: Modified release tablet

S. No.	Ingredient	Quantity (mg/tablet)
1.	Licofelone	300.0
2.	Budesonide	3.0
3.	Lactose	120.0

4.	Sodium starch glycollate	3.0
5.	Hydroxypropyl methylcellulose	67.0
6.	Isopropyl alcohol	q.s. (lost in processing)
7.	Croscarmellose sodium	3.0
8.	Colloidal silicon dioxide	2.0
9.	Magnesium stearate	2.0

Procedure:

i) Licofelone, Budesonide, Lactose & Sodium starch glycollate were mixed together and sifted through mesh #30 sieve.

ii) Hydroxypropyl methylcellulose was dissolved in ingredient Isopropyl alcohol to obtain a homogeneous dispersion.

iii) The material of step (i) was granulated with the material of step (ii) followed by drying and sifting through mesh #24 sieve.

iv) Croscarmellose sodium, Colloidal silicon dioxide & Magnesium stearate were sifted through mesh #40 sieve.

v) The material of step (iv) was mixed with material of step (iii) and compressed into tablets.

Example 9: Sustained Release Bilayered tablets

A) Granules for one layer

S. No.	Ingredient	Quantity (mg/tablet)
1.	Licofelone	300.0
2.	Microcrystalline cellulose	150.0
3.	Hydroxypropyl methylcellulose	45.0
4.	Polyoxyl 40 hydrogenated castor oil	3.0
5.	PVP K-30	5.0
6.	Magnesium stearate	3.0
7.	Colloidal silicon dioxide	3.0
8.	Isopropyl alcohol	q.s. (lost in processing)

Procedure:

i) Licofelone, Microcrystalline cellulose & Hydroxypropyl methylcellulose were mixed together.

ii) Polyoxyl 40 hydrogenated castor oil & PVP K-30 were dissolved in Isopropyl alcohol and granulated the above mixture.

iii) The granules of step (ii) were dried and blended with Magnesium stearate &

Colloidal silicon dioxide.

B) Granules for other layer

S. No.	Ingredient	Quantity (mg/tablet)
1.	Mefenamic acid	200.0
2.	Microcrystalline cellulose	150.5
3.	Maize starch	55.5
4.	Sodium alginate	3.0
5.	Magnesium stearate	3.0
6.	Croscarmellose sodium	4.0
7.	Purified water	q.s. (lost in processing)

Procedure:

i) Mefenamic acid, Microcrystalline cellulose & Maize starch were mixed together.

ii) Sodium alginate dissolved in Purified water was used to granulate the above mixture.

iii) The granules of step (ii) were dried and blended with Magnesium stearate & Croscarmellose sodium.

The granules of **A** and **B** were compressed into bilayered tablets.

Example 10: Oral Liquid

S. No.	Ingredient	Quantity (mg/100 ml)
1.	Licofelone	150.00
2.	Codiene	40.00
3.	Desloratadine	50.00
4.	Citric acid monohydrate	1.50
5.	Hydroxyethyl cellulose	20.00
6.	Sorbitol solution (70% w/v)	50.00
7.	Saccharin sodium	0.50
8.	Sodium benzoate	1.00
9.	Raspberry flavor	q.s. (lost in processing)
10.	Purified water	q.s. to 100 ml

Procedure:

i) Licofelone, Codiene & Desloratadine were sifted through #40 mesh sieve and blended with Hydroxyethyl cellulose passed through #40 mesh sieve.

ii) Citric acid monohydrate, Saccharin sodium, Sodium benzoate, Raspberry flavor and Sorbitol solution were dispersed in Purified water.

iii) The material of step (ii) was added with continuous stirring to the material of step (iii) to obtain a homogeneous suspension.

Example 11: Topical Gel

S. No.	Ingredient	Quantity (g)
1.	Licofelone	2.0
2.	Betamethasone	3.0
3.	Aspirin	0.5
4.	Dimethylacetamide	20.0
5.	Ethyl Alcohol	40.0
6.	Acetone	11.5
7.	Cremophor® RH 40	4.0
8.	Propylene glycol	35.0
9.	Polyethylene glycol 400	48.8
10.	Carbopol 934	4.0
11.	Purified water	30.0
12.	Diethylamine	1.2

Procedure:

i) Dimethylacetamide was mixed with ethyl alcohol and acetone at 30° C with stirring.

ii) To the mixture obtained in step (i), Nimesulide and Betamethasone were added and stirred till completely dissolved.

iii) Propylene glycol, polyethylene glycol 400, aspirin and water were mixed in homogenizer.

iv) To the homogenised mixture obtained in step (iii), 1.5% w/w of carbopol 934 was added slowly under stirring.

v) The mixture obtained in step (ii) was added to the mixture obtained in step (iv) under stirring without vortex formation to avoid aeration preferably under vacuum (25 mm of Hg).

vi) The mixture obtained was neutralized by slow addition of Diethylamine with slow stirring at a temperature of 25-30° C and under vacuum (25 mm of Hg) to affect gel formation.

Example 12: Injection

S. No.	Ingredient	Quantity/ 100 ml
1.	Licofelone	3.3 g

2.	Netilmicin sulfate	1.0 g
3.	Polyethylene glycol (PEG-400)	30.0 ml
4.	Propylene glycol	20.0 ml
5.	Glycine Buffer pH 11.3	36.0 ml
6.	Sodium hydroxide solution 4.0% w/v	11.2 ml

Procedure:

i) Specified quantity of PEG-400 was taken into a vessel.

ii) Propylene glycol was added to step (i) with continuous stirring using mechanical stirrer.

iii) About 30.0 ml of the Glycine Buffer pH 11.3 was added to the step (ii) with continuous stirring to form a homogeneous mixture.

iv) Weighed amount of Nimesulide and Netilmicin sulfate were added to the step (iii) with continuous stirring.

v) Specified quantity of Sodium hydroxide solution 4.0% w/v was added to step (iv) with continuous stirring to form a homogeneous solution.

vi) The solution of step (v) was mixed by continuous stirring.

vii) Remaining quantity of Glycine Buffer pH 11.3 was added to make up volume to 100 ml.

viii) The solution of step (vii) was mixed by continuous stirring.

ix) Final pH to 10.0 was adjusted by adding Sodium hydroxide solution 4.0% w/v to step (viii).

x) The solution of step (ix) was mixed by continuous stirring to obtain the product.

We claim:

1. A pharmaceutical compositions comprising at least one analgesic and anti-inflammatory compound(s) that inhibits both COX and LOX as active agent in combination with at least one another active agent optionally with one or more other pharmaceutically acceptable excipient(s).
2. A composition according to claim 1, wherein the analgesic and anti-inflammatory compound(s) that inhibits both COX and LOX is selected from a group comprising BW 755C, tepoxalin, ER-34122, licofelone, RWJ 63556, SF&F 86002, and the pharmaceutically acceptable salts, esters, conjugate acids, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, prodrugs or mixtures thereof.
3. A composition according to claim 2, wherein the analgesic and anti-inflammatory compound(s) that inhibits both COX and LOX is licofelone or its pharmaceutically acceptable salts, esters, conjugate acids, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, prodrugs or mixtures thereof.
4. A composition according to any of the claims 1-3, wherein the another active agent(s) is selected from a group comprising antipyretics, aldosterone receptor antagonists, antibiotics, enzymes, antimuscarinic agents, anti-viral agents, protein kinase inhibitors, α2-adrenergic agonist, ACE inhibitors, opioid analgesics, steroids, leukotriene B_4(LTB_4) antagonists, leukotriene A_4(LTA_4) hydrolase inhibitors, 5-HT agonists, HMG CoA reductase inhibitors, H_2 antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, decongestants, diuretics, anti-histamines, inducible nitric oxide synthase inhibitors, antivirals, antihistamines, Helicobacter pylori inhibitors, bronchodilators, spasmolytics, muscle relaxants, proton pump inhibitors, isoprostane inhibitors, PDE4-inhibitors, NSAIDs, selective or preferential COX-2 inhibitors, COX-1 inhibitors, expectorants, analgesics, antiemetics, urinary acidifiers, antidepressants, antipsychotics, antimigraine agents, enzymes, and like, or mixtures thereof.
5. A composition according to claim 4, wherein the enzyme is selected from a group comprising serratiopeptidase, trypsin, chymotrypsin, and pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.
6. A composition according to claim 4, wherein the antimuscarinic agent is selected from a group comprising alvameline chloride, bethanechol chloride, darifenacin chloride,

dicyclomine hydrochloride, emepronium carrageenate, hyoscyamine sulfate, imipramine hydrochloride, oxybutynin chloride, S-oxybutynin chloride, propantheline bromide, propiverine chloride, revatropate chloride, temiverine chloride, terodiline chloride, tolterodine tartrate, trospium chloride, vamicamide chloride, zamifenacin chloride, AH-9700, FK-584, J-104135, KRP-197, YM905, and YM-46303, and pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

7. A composition according to claim 4, wherein the antiviral agent is selected from a group comprising ganciclovir, foscarnet, cidofovir, acycloguanosine, trifluorothymidine, acyclovir, famciclovir, abacavir, oseltamivir, stavudine, interferon alfa, atevirdine, efavirenz, ribavirin, ritonavir, rimantidine, amantidine, didanosine, vidarabine and valaciclovir, and pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or combination thereof.

8. A composition according to claim 4, wherein α2-adrenergic agonist is selected from clonidine, tizanidine, UK14304, brimonidine, apraclonidine, guanfacine, guanabenz, phenylephrine, methoxamine, metaraminol, ephedrine, oxymetazoline, naphazoline, tetrahydrozoline, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

9. A composition according to claim 4, wherein the ACE inhibitor is selected from benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril and trandolapril, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

10. A composition according to claim 4, wherein the opioid analgesic is selected from a group comprising alfentanil, allylprodine, alphaprodine, anileridine, 3-benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narcine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone,

oxymorphone, papaveretum, pentazocine, phenadoxone, phenmorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, and pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

11. A composition according to claim 4, wherein the steroid is selected from a group comprising cortisone, cortisol, corticosterone, hydrocortisone, hydrocortisol, prednisone, prednisolone, dexamethasone, beclomethasone, betamethasone, mometasone, budesonide, triamcinolone acetonide, fluticasone, ciclesonide, betametasone, and pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

12. A composition according to claim 4, wherein the LTB_4 receptor antagonist is selected from a group comprising ebselen, linazolast, ontazolast, Bay-x-1005, BI-RM-270, CGS-25019C, ETH-615, TMK-688, LY 213024, LY 210073, LY 223982, LY 233469, LY 255283, LY 264086, LY 292728 and LY 293111; ONO-LB457, ONO-4057, and ONO-LB-448, S-2474, calcitrol, PF 10042, RP 66153, SC-53228, SC-41930, SC-50605, SC-51146, SC-53228, SB-201146, SB-209247, SKF-104493, SM 15178, TMK-688, BPC-15, and pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

13. A composition according to claim 4, wherein the leukotriene A_4 (LTA_4) hydrolase inhibitor is selected from a group comprising RP-64966, (S,S)3-amino(4-benzyloxyphenyl)hydroxybutyric acid benzyl] ester, N-(2(R)-(cyclohexylmethyl) (hydroxycarbamoyl)propionyl)-L-alanine, 7-(4-(4-ureidobenzyl)phenyl) heptanoic acid and 3-(3(IE,3E-tetradecadienyl) oxiranyl)benzoic acid lithium salt, and pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

14. A composition according to claim 4, wherein the 5-HT agonist is selected from rizatriptan, sumatriptan, naratriptan, zolmitriptan, eleptriptan, almotriptan, ergot alkaloids, L-741604, SB-220453, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

15. A composition according to claim 4, wherein the H_2 antagonist is selected from a group comprising cimetidine, roxatidine, ranitidine, famotidine, and pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric

forms, or mixtures thereof.

16. A composition according to claim 4, wherein the antineoplastic agent is selected from a group comprising cortisone, cortisol, corticosterone, hydrocortisone, hydrocortisol, prednisone, prednisolone, dexamethasone, beclomethasone, betamethasone, mometasone, budesonide, triamcinolone acetonide, fluticasone, ciclesonide, betametasone, and pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

17. A composition according to claim 4, wherein the antiplatelet agent is selected from a group comprising aspirin, ticlopidine, dipyridamole, clopidogrel, glycoprotein 11b/111a receptor antagonists, and pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

18. A composition according to claim 4, wherein the decongestant is selected from a group comprising phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, epinephrine, naphazoline, xylometazoline, propylhexedrine, levodesoxyephedrine, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof.

19. A composition according to claim 4, wherein the diuretic is selected from a group comprising amanozine, amiloride, arbutin, chlorazanil, ethacrynic acid, etozolin, hydracarbazine, isosorbide, mannitol, metochalcone, muzolimine, ticrynafen, triamterene, bendroflumethiazide, chlorothiazide, furosemide, and pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

20. A composition according to claim 4, wherein the proton pump inhibitor is selected from a group comprising omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole, and pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

21. A composition according to claim 4, wherein the PDE_4-inhibitor is selected from a group comprising CDC-998, IC-485, CC-1088, SCH351591, V11294A, AWD-12-281, AWD-12-343, Cipamfylline, Atizoram, CDC-801, Lirimilast, Piclamilast, Cilomilast, and Roflumilast, and pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

22. A composition according to claim 4, wherein the antihistamine is selected from

astemizole, azatadine, brompheniramine, buclizine, carbinoxamine, cetirizine, chlorpheniramine, clemastine, cyclizine, cyproheptadine, dexchlorpheniramine, dimenhydrinate, diphenhydramine, diphenylpyraline, doxylamine, fexofenadine, hydroxyzine, loratadine, meclizine, methapyrilene, methdilazine, orphenadrine, pheniramine, promethazine, pyrilamine, terfenadine, trimeprazine, tripelennamine, triprolidine or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

23. A composition according to claim 4, wherein the NSAID is selected from aceclofenac, diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, meclofenamate, naproxen, nimesulide, phenylbutazone, piroxicam, sulindac, suprofen, tolmetin, indomethacin, or pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

24. A composition according to claim 4, wherein the COX-2 inhibitor is selected from a group comprising celecoxib, rofecoxib, valdecoxib, COX 189, etoricoxib, and pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

25. A composition according to claim 4, wherein the bronchodilator is selected from a group comprising fenoterol, metaproterenol, procaterol, salbutamol, terbutaline, ipratropium bromide, and pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

26. A composition according to claim 4, wherein the muscle relaxant is selected from a group comprising robaxin, robaxisal, succinylcholine, tizanidine, tubocurarine, metocurine, atracurium, cisatracurium, mivacurium, doxacurium, pancuronium, vercuronium, pipecuronium, rocuronium, gallamine, cyclobenzaprine, and pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.

27. A composition according to claim 1, wherein the one or more pharmaceutically acceptable excipients are selected from a group comprising binders, disintegration agents, fillers or diluents, stabilizers, lubricants, wetting agents, anti-adherents or glidants, solubilizers, carriers, antioxidants, vehicles, buffers, preservatives, complexing agents, colorants, flavorants, pH modifiers, surfactants, viscosifiers, gelling agents, tonicity modifiers, lipid component, emulsifiers, coating agents, plasticizers, organic solvents, and chelating agents, either alone or in combination thereof.

28. A process for the preparation of pharmaceutical composition according to claim 1, which comprises optionally treating the active agent that inhibits both COX and LOX and at least one another active agent with one or more pharmaceutically acceptable excipient(s) and formulation into a suitable dosage form.

29. A method of using the pharmaceutical composition according to claim 1 for the management of inflammation, pain and other associated disorders, which comprises administering to a subject in need thereof an effective amount of the composition.

30. A method according to claim 29, wherein the composition according to claim 1 is useful in the management of inflammation, pain and other associated disorders selected form the group comprising muscle tightness or spasms, viral infections such as cold and cough, allergic manifestations such as allergic rhinitis, skin rashes with or without swelling, arthritis, asthma, angina, inflammatory bowel disease, Crohn's disease, migraine headaches, Alzheimer's disease, stroke, ischemia and trauma, gastric ulcer induced pain, intermittent or episodic pain, angiogenesis, viral infections, cardiovascular diseases, neoplasia, cancer, bacterial infections, urinary incontinence condition, and angiogenesis.

31. Use of the composition according to claim 1 comprising at least one analgesic and anti-inflammatory compound(s) that inhibits both COX and LOX with at least one another active agent for the manufacture of a medicament for the management of inflammation, pain and other associated disorders.

32. Use according to claim 31, for the management of inflammation, pain and other associated disorders selected form the group comprising muscle tightness or spasms, viral infections such as cold and cough, allergic manifestations such as allergic rhinitis, skin rashes with or without swelling, arthritis, asthma, angina, inflammatory bowel disease, Crohn's disease, migraine headaches, Alzheimer's disease, stroke, ischemia and trauma, gastric ulcer induced pain, intermittent or episodic pain, angiogenesis, viral infections, cardiovascular diseases, neoplasia, cancer, bacterial infections, urinary incontinence condition, and angiogenesis.

33. The pharmaceutical composition and process for the preparation substantially as herein described and illustrated by the examples.

Figure-1: Isobologram showing analgesic effect of licofelone and nimesulide in acetic acid-induced writhing in mice

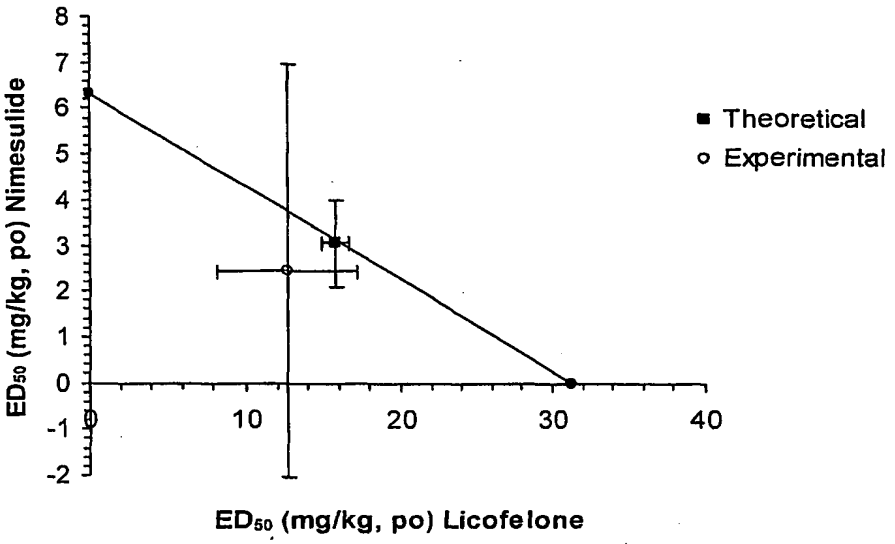

Figure-2: Effect of combination of licofelone (Lico) and serratiopeptidase (Serr) against acetic acid-induced writhing in mice

P<0.05 as compared to control group; Values in the parenthesis represent dose (mg/kg) (N=3-4)